Platform: Computational Methods

178-Plat
Modeling Proteins and Small Molecules with Inhomogeneous Dielectric Function: Implementation in Delphi
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Most implicit solvent models treat bio-molecules as homogeneous dielectric medium inside high dielectric water phase. However, the dielectric distribution inside biological macromolecules is non-homogeneous, which depends on various factors, such as amino acid composition, structure, packing and flexibility. Many approaches have been developed to model the inhomogeneous dielectric distribution in biomolecules, including amino acid specific dielectric constant, using non-typical probe radius in finite-difference algorithm or delivering the dielectric constant from Gaussian distribution of atomic densities. Here, in DelPhi program, we developed an inhomogeneous dielectric method based on Gaussian smooth function. We tested this new method on calculating the solvation energies of 504 small molecules and the results show the method achieves better accuracy of the solvation energy calculation than homogeneous dielectric methods. Other tests on real proteins demonstrate that our inhomogeneous dielectric method is more reliable than homogeneous dielectric method for pKa and electrostatic potential calculations.

179-Plat
Introducing Charge Hydration Asymmetry in the Realm of Continuum Solvation
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Charge hydration asymmetry (CHA) manifests itself in the experimentally observed strong dependence of free energy of ion hydration on the sign of the ion charge. This asymmetry is not consistently accounted for by popular models of solvation; its magnitude varies greatly between the models. While it is clear that CHA is somehow related to charge distribution within a water molecule, the exact nature of this relationship is unknown. We propose a simple, yet general and rigorous criterion that relates rotational and charge inversion properties of a water molecule's charge distribution with its ability to cause CHA. We show which electric multipole components of a water molecule are key to explain its ability for asymmetric charge hydration. We then test several popular water models and explain why specific models show none, little, or strong CHA in simulations. We use the gained insight to derive an analogue of the Born equation that includes the missing physics necessary to account for CHA and does not rely on redefining the continuum dielectric boundary. The proposed formula is as simple as the original, does not contain any fitting parameters, and predicts hydration free energies and entropies of spherical cations and anions within experimental uncertainty. We further incorporate CHA into the framework of Generalized Born continuum solvation model; our findings suggest that the gap between the practical continuum electrostatics framework and the more fundamental explicit solvent treatment can be reduced considerably by explicitly introducing CHA into the existing framework.

180-Plat
Enhanced Sampling Assisted Flexible Fitting of Atomic Structures into Electron Microscopy Maps
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For many problems in structural biology, flexible-fitting computational algorithms are often useful in interpreting low-resolution electron microscopy (EM) maps of macromolecular assemblies. A widely used atomistic simulation technique is molecular dynamics flexible fitting (MDFF), which has been applied to generate structural models of large complexes. All-atom explicit-solvent MDFF simulations are not only computationally demanding, but also can be sensitive to the resolution of the target EM map. Moreover, functional movements of many biomolecules require large-scale conformational reorganization elicited via domain translations/rotations, where methods such as MDFF may be limited in capturing the rotations of structural elements. To decrease the computational cost and alleviate the limitations stemming from domain orientations, one can combine MDFF with an enhanced sampling technique to accelerate the conformational search in a single atomistic simulation. In this work, we judiciously combine MDFF with temperature-accelerated molecular dynamics (TAMD), an enhanced sampling method, and carry out TAMD-assisted MDFF (TAMDFF) simulations of proteins and nucleic acids. We find that TAMDFF simulations can achieve target structures of similar quality as MDFF on short timescales. In some cases, only TAMDFF simulations are able to capture conformational changes likely because MDFF simulations are unable to overcome the underlying free-energy barriers. We suggest that TAMDFF may be a viable strategy for structural refinement of large ribonucleoprotein complexes such as the ribosome.

181-Plat
SAXS/WAXS Intensities and Pair-Distance Distribution Functions from Molecular Dynamics Simulations
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Solution scattering experiments on biological macromolecules measure one-dimensional intensity profiles that serve as signatures of the underlying three-dimensional atomistic structure. For X-rays, these intensities are Fourier transforms of the electron pair-distance distribution function (PDDF). The PDDFs contain the maximum amount of information accessible in such experiments, and they greatly aid in the interpretation of the scattering data. Because of this fundamental and practical importance of the PDDFs, inverse Fourier transform methods are commonly applied to obtain the PDDFs from the measured scattering data. However, these transforms are limited by the finite range of scattering angles probed in experiments and by statistical uncertainties. By contrast, in molecular dynamics simulation the real space information is directly accessible. We developed a method to calculate the PDDFs from atomistic structures, together with accurate scattering intensities in both SAXS and WAXS regimes. For a selection of proteins, we first show that the calculated scattering intensities are in excellent agreement with precise measurements. We then demonstrate that a q-range up to 2-3 Å-1 in the WAXS regime is sufficient to resolve most of the features of the exact PDDFs, providing guidance for the design of scattering experiments.

182-Plat
Strategies for Model Reduction in DCA-Based Multibody Modeling of Biopolymers
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Numerical simulations of bio-polymeric systems are most often limited by their inherent size and complexity. As such, models with varying degree of fidelity, ranging from fully atomistic to continuum scale, are employed by researchers to study these systems. In reality, such complex molecular systems exhibits important physical phenomenon at multiple spatial and temporal scales. Moreover, characteristics of different sub-domains within a system are prone to change with time. In such systems, it is highly desirable that the hierarchy of reduced order (multiple scale) models be produced which can adaptively track and predict the behavior of the system while maintaining both accuracy and speed. Therefore, it is imperative that computationally intelligent and efficient numerical schemes are developed which can adaptively put effort where required.
The divide and conquer (DCA) based family of multi-body dynamics algorithms has the potential to circumvent many problems associated with the simulations of complex molecular systems. This is achieved through modeling molecular systems as reduced order multi-rigid or multi-flexible body systems. Such approaches have shown to significantly lessen the model complexity while accurately capturing the overall conformational motion and important system behavior. Furthermore, the DCA based algorithms allow the transitions between different resolution models through removing or adding degrees of freedom (dofs), on-the-fly, during simulation with an overall low computational cost [O(log(n))]. This work examines the challenges involved with the adaptive reduction in the model resolution within the DCA framework. The energy, momentum and temperature issues associated with removing single dof at a time are compared with instantaneous locking of multiple dofs. Numerical examples are presented that include both multi-rigid and multi-flexible body models and the results are compared for physically meaningful state of the system from both sequential and instantaneous transitions.

183-Plat
A Simple Coarse-Grained Model to Map the Transition Pathway Between Two Stable Conformations using the Anisotropic Elastic Network Model
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